Please replace the first paragraph of the specification, at page 1, lines 5-7, with the following rewritten paragraph:

A1

This application is a divisional of U.S. Application Ser. No. 09/300,328, filed April 27, 1999, now U.S. Patent No. 6,294,169, which is a divisional of U.S. Application Ser. No. 08/852,936, filed May 8, 1997, now U.S. Patent No. 6,010,878, which claims the benefit of U.S. Provisional Application Nos. 60/018,961 filed June 5, 1996, 60/020,344 filed May 23, 1996 and 60/017,949 filed May 20, 1996.

Please replace the paragraph beginning at page 4, line 24, with the following rewritten paragraph:

A2

Toward these ends, and others, it is an object of the present invention to provide polypeptides, inter alia, that have been identified as novel ICE LAP-6 by homology between the amino acid sequence set out in Figure 1 or the polypeptide encoded by the deposited clone and known amino acid sequences of other proteins such as those sequences set out in Figures 2A-2C.

Please replace the two paragraphs beginning at page 5, line 1, with the following rewritten paragraphs:

A3

In a particular preferred embodiment of this aspect of the invention the polynucleotide comprises the region encoding human ICE LAP-6 set forth in Figures 2A-2C.

In accordance with this aspect of the present invention there is provided an isolated nucleic acid molecule encoding a mature polypeptide expressed by the human cDNA in Figures 2A-2C or derived using the primers set forth in Example 1, or a polynucleotide encoding the polypeptide in Figure 1 or derived from the polypeptide encoded by the deposited clone.

Please replace the seven paragraphs beginning at page 8, line 4, deleting the paragraph at page 8, lines 7-12, with the following six rewritten paragraphs:

A4

Figure 1 [SEQUENCE ID NO. 1] shows the predicted amino acid sequence of human ICE LAP-6. The active site pentapeptide QACGG (SEQ ID NO:11) is underlined. Putative amino acid (Asp) cleavage sites are indicated with bold letters.

Figures 2A-2C [SEQUENCE ID NO. 2] show a nucleic acid sequence of human ICE LAP-6.

Figure 4 [SEQUENCE ID NO. 3] shows a nucleic acid sequence variant derived from human ICE LAP-6.

Figure 4 [SEQUENCE ID NO. 4] shows an amino acid sequence variant derived from human ICE LAP-6.

Figure 5 shows phylogenetic analysis of the ICE/ced-3 gene family.

Figure 6 shows MCF7 the results of an analysis of breast carcinoma cells transiently transfected demonstrating that over-expression of ICE LAP-6 induces cell death in mammalian cells.

Please replace the paragraph beginning at page 17, line 2, with the following rewritten paragraph:

The present invention relates to novel ICE LAP-6 polypeptides and polynucleotides, among other things, as described in greater detail below. In particular, the invention relates to polypeptides and polynucleotides of a novel human ICE LAP-6, which is related by amino acid sequence homology to human interleukin-1 beta converting enzyme apoptosis protease polypeptides. The invention relates especially to ICE LAP-6 having the nucleotide and amino acid sequences set out in Figures 1 and 2A-2C respectively. It will be appreciated that the nucleotide and amino acid sequences set out in Figures 2A-2C and 1 respectively, were obtained by sequencing the cDNA obtained from a human K562 (erythroleukemia) cell line cDNA library.

Please replace the paragraph beginning at page 17, line 28, with the following rewritten paragraph:

Human ICE LAP-6 of the invention is structurally related to other proteins of the human interleukin-1 beta converting enzyme apoptosis protease family, as shown by the results of sequencing the cDNA encoding human ICE LAP-6 in Figure 1. The cDNA of Figures 2A-2C was obtained as described in Example 1. The polypeptide of Figure 1 and the polypeptide encoded by the deposited clone each are proteins which have a deduced molecular weight of about 45.8 kDa.

Please replace the paragraph beginning at page 18, line 9, with the following rewritten paragraph:

B7 The coding sequence which encodes the polypeptide may be identical to the coding sequence of the polynucleotide derived using the primers set forth in Example 1, or the polynucleotide of Figures 2A-2C. It also may be a polynucleotide with a different sequence, which, as a result of the redundancy (degeneracy) of the genetic code, encodes the polypeptide of the cDNA of Figure 1 or the polypeptide encoded by the deposited clone.

Please replace the paragraph beginning at page 20, line 28, with the following rewritten paragraph:

B8 Particularly preferred embodiments in this respect, moreover, are polynucleotides which encode polypeptides which retain substantially the same biological function or activity as the mature polypeptide encoded by the cDNA of Figures 2A-2C encoded by the polynucleotide sequence of the deposited clone, or derived using the primers set forth in Example 1.

Please replace the paragraph beginning at page 25, line 19, with the following rewritten paragraph:

B9 Also among preferred embodiments of this aspect of the present invention are polypeptides comprising fragments of ICE LAP-6, most particularly fragments of the ICE LAP-6 having the amino acid set out in Figure 1 or the amino acid sequence of the polypeptide encoded by the deposited clone, and fragments of variants and derivatives of the ICE LAP-6 of Figure 1 or the polypeptide encoded by the deposited clone, such as, for example the amino acid sequence of Figure 4.

Please replace the paragraph beginning at page 27, line 25, with the following rewritten paragraph:

B10 Further preferred regions are those that mediate activities of ICE LAP-6. Most highly preferred in this regard are fragments that have a chemical, biological or other activity of ICE LAP-6, including those with a similar activity or an improved activity, or with a decreased undesirable activity. Highly preferred in this regard are fragments that contain regions that are homologs in sequence, or in position, or in both sequence and to

active regions of related polypeptides, such as the related polypeptides set out in Figures 2A-2C, which include human interleukin-1 beta converting enzyme apoptosis proteases. Among particularly preferred fragments in these regards are truncation mutants, as discussed above.

Please replace the paragraph beginning at page 28, line 3, with the following rewritten paragraph:

It will be appreciated that the invention also relates to, among others, polynucleotides encoding the aforementioned fragments, polynucleotides that hybridize to polynucleotides encoding the fragments, particularly those that hybridize under stringent conditions, and polynucleotides, such as PCR primers, for amplifying polynucleotides that encode the fragments. In these regards, preferred polynucleotides are those that correspondent to the preferred fragments, as discussed above. Preferred polynucleotides fragments may be derived from the sequences of Figures 2A-2C.

Please replace the paragraph beginning at page 54, line 28, with the following rewritten paragraph:

Members of the ICE/ced-3 gene family are belived to be effector components of the cell death machinery. Herein this Example, a novel member of this family designated ICE LAP-6 is characterized. By phylogenetic analysis, ICE LAP-6 is classified into the Ced-3 subfamily which includes Ced-3, Yama/CPP32/apopain, Mch2 and ICE LAP-3/Mch3/CMH-1. ICE LAP-6 contains an active site QACGG (SEQ ID NO:11) pentapeptide, rather than the QACRG (SEQ ID NO:10) pentapeptide shared by other family members. Overexpression of ICE LAP-6 induces apoptosis in MCF7 breast carcinoma cells. ICE LAP-6 is also proteolytically processed into an active cysteine protease by granzyme B, an important component of cytotoxic T cell-mediated apoptosis. Once activated, ICE LAP-6 is able to cleave the death substrate poly (ADP-ribose) polymerase (PARP) into signature apoptotic fragments.

Please replace the paragraph beginning at page 58, line 11, with the following rewritten paragraph:

A blast search of GenBank protein data base revealed that the predicted protein sequence of ICE LAP-6 has significant similarity to the members of the ICE/Ced-3

family, particularly in the regions corresponding to the active subunits of ICE (Thomberry, N. A.,et al (1992) Nature 356, 768-774). In this region, ICE LAP-6 shares 31% sequence identity (55% sequence similarity) with the C. elegans CED-3 protein, 33% identity (52% sequence similarity) with ICE-LAP3, 30% identity (56% similarity) with Mch2a and 29% sequence identity (52% similarity) with Yama. ICE LAP-6 also has 25%-28% sequence identity with ICE and the ICE-related genes, ICE rel II and ICE rel III. Phylogenetic analysis of the ICE/ced-3 gene family showed that ICE LAP-6 is a member of the Ced-3 subfamily which includes Yama, ICE-LAP3, and Mch2 (Figure 5). Like Ced-3, ICE LAP-6 contains a long N-terminal putative prodomain. Based on the x-ray crystal structure of ICE (Walker, N. P. C. et al, (1994) Cell 78, 343-352; Wilson, K. P., et al (1994) Nature 370, 270-275), the amino acid residues His237, Gly238, Cys285 of ICE are involved in catalysis, while the residues Arg179, Gln283 and Arg341 form a binding pocket for the carboxylate side chain of the P1 aspartic acid. These six residues are conserved in all ICE/Ced-3 family members thus far cloned as well as in ICE LAP-6. However, residues that form the P2-P4 binding pockets are not widely conserved among family members, suggesting that they may determine substrate specificity. Surprisingly, ICE LAP-6 contains a unique active site pentapeptide QACGG (SEQ ID NO:11), instead of the QACRG (SEQ ID NO:10) shared by other family members Figures 2A-2C).

Please replace the paragraph beginning at page 59, line 10, with the following rewritten paragraph:

To study the functional role of ICE LAP-6, MCF7 breast carcinoma cells were transiently transfected with an expression vector encoding the full-length ICE LAP-6 protein (ICE LAP-6-flag) and subsequently assessed for apoptotic features. Like the other ICE/Ced-3 family members, expression of ICE LAP-6 caused cell death (Figure 6) The ICE LAP-6-transfected MCF7 cells displayed morphological alterations typical of adherent cells undergoing apoptosis, becoming rounded, condensed, and detaching from the dish. ICE LAP-6 induced apoptosis was inhibited by the broad spectrum ICE inhibitor z-VAD fmk (Pronk, G. J., (1996) Science 271, 808-810). To determine whether the amino acid residue Cys286, corresponding to the catalytic Cys285 of ICE, was essential for apoptotic activity, a mutant form of ICE LAP-6 was generated in which the cysteine residue was altered to an alanine. MCF7 breast carcinoma cells were transiently transfected with the reporter gene b-galactosidase and either C-terminal flag-tagged ICE